ClinicalEvidence

Pelvic inflammatory disease

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ABSTRACT

INTRODUCTION: Pelvic inflammatory disease is caused by infection of the upper female genital tract and is often asymptomatic. Pelvic inflammatory disease is the most common gynaecological reason for admission to hospital in the US, and is diagnosed in approximately 1% of women aged 16 to 45 years consulting their GP in England and Wales. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: How do different antimicrobial regimens compare when treating women with confirmed pelvic inflammatory disease? What are the effects of routine antibiotic prophylaxis to prevent pelvic inflammatory disease before intrauterine contraceptive device (IUD) insertion? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up to date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 13 RCTs or systematic reviews of RCTs that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: antibiotics (oral, parenteral, different durations, different regimens) and routine antibiotic prophylaxis (before intrauterine device insertion in women at high risk or low risk).

QUESTIONS

INTERVENTIONS

TREATMENT: WHICH ANTIBIOTIC?

Likely to be beneficial

ANTIBIOTIC PROPHYLAXIS BEFORE IUD

Unknown effectiveness

Unlikely to be beneficial

Key points

- Pelvic inflammatory disease (PID) is caused by infection of the upper female genital tract, and is often asymptomatic.

  PID is the most common gynaecological reason for admission to hospital in the US, and is diagnosed in 1.1% of women aged 16 to 45 years consulting their GP in England and Wales.

  Epithelial damage from infections such as *Chlamydia trachomatis* or *Neisseria gonorrhoeae* may allow opportunistic infection from many other bacteria.

  About 20% of women with PID become infertile, 40% develop chronic pain, and 1% of women who conceive have an ectopic pregnancy.

  Spontaneous resolution of symptoms may occur in some women.

  Empirical treatment is started as soon as the diagnosis of PID is suspected to minimise the risk of sequelae such as tubal obstruction and infertility.

  The positive predictive value of clinical diagnosis is 65% to 90% compared with laparoscopy, and observational studies suggest that delaying treatment by three days may impair fertility.

  The absence of infection from the lower genital tract does not exclude a diagnosis of PID.

- Oral antibiotics are likely to be beneficial, and are associated with the resolution of symptoms and signs of pelvic infection, but we don't know which antibiotic regimen is best.

  Clinical and microbiological cure rates of 88% to 100% have been reported after oral antibiotic treatment.

  The risks of tubal occlusion and infertility depend on severity of infection before treatment. Clinical improvement following treatment may not necessarily translate into improved long-term fertility .

- Oral antibiotics may be as effective as parenteral antibiotics in reducing symptoms and preserving fertility in women with mild to moderate PID, with fewer adverse effects. However, we don't know the optimal duration of treatment.

- Women at high risk for PID include those with prior infection with *C trachomatis* or *N gonorrhoeae*, young age at onset of sexual activity, unprotected sexual intercourse with multiple partners, and prior history of PID. Risks of PID may be increased after instrumentation of the cervix, and testing for infection before such procedures is advisable. We don't know whether prophylactic antibiotics before IUD insertion reduce these risks.

Clinical context

GENERAL BACKGROUND

Pelvic inflammatory disease (PID) is a common cause of morbidity in young women, usually occurring as a consequence of sexually transmitted infection. Chlamydia and gonorrhoea are the commonest recognised causes but in the majority of cases no pathogen is identified. Treatment is with broad spectrum antibiotics which are associated with high rates of short term improvement, but despite treatment there is an increased risk of tubal damage leading to chronic pelvic pain and infertility.

FOCUS OF THE REVIEW

The main focus of this review is on which antimicrobial regimens are most effective in the treatment of pelvic inflammatory disease and how long treatment should be given for. The review also assesses the rate of adverse events associated with different treatment regimens, and whether prophylactic antibiotics prior to the insertion of an intrauterine contraceptive device are effective in preventing PID. The timing of when to start antibiotics (before or after the results of microbiology test are available) is not assessed because of lack of evidence found in the previous version of this *Clinical Evidence* overview and current expert opinion that treatment should not be delayed.

COMMENTS ON EVIDENCE

We identified a large number of randomised controlled trials comparing different treatment regimens for pelvic inflammatory disease, but the majority were small and of low quality. A small number of large well conducted trials and one systematic review were available. Specific limitations included short term follow up limited to a few weeks, and difficulties in making an objective diagnosis of pelvic inflammatory disease.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this review was carried out from the date of the last search, May 2007 to September 2013. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 97 studies. After de-duplication and removal of conference abstracts, 35 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 27 studies and the further review of 8 full publications. Of the 8 full articles evaluated, 1 systematic review and 3 RCTs were added at this update.

DEFINITION

Pelvic inflammatory disease (PID) is inflammation and infection of the upper genital tract in women, typically involving the uterus and adnexae. Mild-to-moderate PID is defined as the absence of a tubo-ovarian abscess. Severe disease is defined as severe systemic symptoms or the presence of tubo-ovarian abscess. [1]

INCIDENCE/ PREVALENCE

The exact incidence of PID is unknown because the disease cannot be diagnosed reliably from clinical symptoms and signs. [2] [3] [4] Direct visualisation of the fallopian tubes by laparoscopy is the best single diagnostic test, but it is invasive, lacks sensitivity, and is not used routinely in clinical practice. PID is the most common gynaecological reason for admission to hospital in the US, accounting for 18/10,000 recorded hospital discharges. [5] A diagnosis of PID is made in 1.1% of women aged 16 to 45 years attending their primary-care physician in England and Wales. [6] However, because most PID is asymptomatic, this figure under-estimates the true prevalence. [2] [7] A crude marker of PID in resource-poor countries can be obtained from reported hospital admission rates, where it accounts for 17% to 40% of gynaecological admissions in sub-Saharan Africa, 15% to 37% in Southeast Asia, and 3% to 10% in India. [8]

AETIOLOGY/ RISK FACTORS

Factors associated with PID mirror those for STDs — young age, reduced socioeconomic circumstances, lower educational attainment, and recent new sexual partner. [3] [9] [10] Women considered at high risk for PID include those with prior infection with chlamydia or gonorrhoea, young age at onset of sexual activity, unprotected sexual intercourse with multiple partners, and prior history of PID. [1] Infection ascends from the cervix, and initial epithelial damage caused by bacteria (especially *Chlamydia trachomatis* and *Neisseria gonorrhoeae*) may allow the opportunistic entry of other organisms. Many different microbes, including *Mycoplasma genitalium* and anaerobes, may be isolated from the upper genital tract. [11] [12] The spread of infection to the upper genital tract can be increased by instrumentation of the cervix, but reduced by barrier methods of contraception,

levonorgestrel implants, and by oral contraceptives compared with other forms of contraception. [13] [14] [15] [16] [17]

PROGNOSIS

PID has a high morbidity; about 20% of affected women become infertile, 40% develop chronic pelvic pain, and 1% of those who conceive have an ectopic pregnancy (see table 1, p 25). [1] [18] Uncontrolled observations suggest that clinical symptoms and signs resolve in a significant proportion of untreated women. [1]

AIMS OF INTERVENTION

To alleviate the pain and systemic malaise associated with infection; to achieve microbiological cure; to prevent development of permanent tubal damage with associated sequelae, such as chronic pelvic pain, ectopic pregnancy, and infertility; and to prevent the spread of infection to others, with minimal adverse effects.

OUTCOMES

Cure rate (includes clinical cure rate; microbiological cure of the upper genital tract; resolution of acute symptoms and signs); **symptom severity** (includes reduction of chronic pelvic pain); **rate of ectopic pregnancy**; **fertility** (includes pregnancy [other than ectopic]); **rate of transmission to others**; **recurrence**; **quality of life**; and **adverse effects of treatment**; *in question on routine antibiotic prophylaxis*: **rate of PID**.

METHODS

Clinical Evidence search September 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2013, Embase 1980 to September 2013, and The Cochrane Database of Systematic Reviews, issue 2, 2013 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published systematic reviews and RCTs, at least single-blinded, and containing 20 or more individuals of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs, where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA, the EMA, and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 27). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **How do different antimicrobial regimens compare when treating women with confirmed pelvic inflammatory disease?**

OPTION **ANTIBIOTICS FOR SYMPTOMS AND MICROBIOLOGICAL CLEARANCE IN WOMEN WITH CONFIRMED PELVIC INFLAMMATORY DISEASE**

- For GRADE evaluation of interventions for Pelvic inflammatory disease, see table, p 27 .
- There is consensus that antibiotic treatment is more effective than no treatment for women with confirmed PID.

Benefits and harms

Different antibiotics versus each other:

We found one systematic review (search date 2004, 34 RCTs, 3548 women) [19] and four subsequent RCTs [20] [21] [22] [23] assessing the effects of different antibiotic regimens in the treatment of pelvic inflammatory disease (PID). The review assessed standard antibiotic regimens and non-standard regimens; see table 2, p 25 for 'standard' and

'non-standard' regimens, as defined by the review. [19] The review identified no RCTs comparing standard or non-standard regimens versus placebo (see Comment section).

Cure rate

Different antibiotics compared with each other We don't know how different antibiotic regimens compare with each other at improving cure rates in women with confirmed pelvic inflammatory disease (PID) (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rate					
[24] RCT	33 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 15/15 (100%) with ofloxacin (oral then IV) plus metronidazole 7/18 (39%) with clindamycin plus gentamicin	RR 1.06 95% CI 0.95 to 1.18 The review reported that overall trial quality was poor	⟷	Not significant
[25] RCT	115 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 46/55 (84%) with cefoxitin plus doxycycline 52/60 (87%) with clindamycin plus gentamicin	RR 0.97 95% CI 0.83 to 1.12 The review reported that overall trial quality was poor	⟷	Not significant
[26] RCT	198 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 75/94 (80%) with cefoxitin plus doxycycline 87/104 (84%) with clindamycin plus gentamicin	RR 0.95 95% CI 0.84 to 1.09 The review reported that overall trial quality was poor	⟷	Not significant
[27] RCT	130 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 64/67 (96%) with cefoxitin plus doxycycline 57/63 (90%) with clindamycin plus gentamicin	RR 1.06 95% CI 0.96 to 1.16 Overall effect size RR 1.01 95% CI 0.93 to 1.08 The review reported that overall trial quality was poor	⟷	Not significant
[28] RCT	131 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 49/64 (77%) with ceftriaxone plus doxycycline 57/67 (85%) with ciprofloxacin plus clindamycin	RR 0.90 95% CI 0.76 to 1.07 The review reported that overall trial quality was poor	⟷	Not significant
[29] RCT	148 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 73/75 (97%) with cefoxitin plus doxycycline 70/73 (96%) with clindamycin plus tobramycin	RR 1.02 95% CI 0.96 to 1.08 The review reported that overall trial quality was poor	⟷	Not significant
[30] RCT	249 women In review [19] See Further information on studies for full details of	**Cure rate** 75/121 (62%) with cefoxitin plus probenecid plus doxycycline 80/128 (63%) with ofloxacin	RR 0.99 95% CI 0.82 to 1.20 The review reported that overall trial quality was poor	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	population included in review				
[31] RCT	62 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 30/31 (97%) with cefoxitin plus doxycycline 28/31 (90%) with clindamycin plus amikacin	RR 1.07 95% CI 0.94 to 1.22 The review reported that overall trial quality was poor	⟷	Not significant
[32] RCT	79 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 38/40 (95%) with cefoxitin plus doxycycline 36/39 (92%) with clindamycin plus tobramycin	RR 1.03 95% CI 0.98 to 1.08 The review reported that overall trial quality was poor	⟷	Not significant
[33] RCT	72 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 34/35 (97%) with cefoxitin plus probenecid plus doxycycline 35/37 (95%) with ofloxacin	RR 1.03 95% CI 0.93 to 1.13 Overall effect size RR 1.02 95% CI 0.97 to 1.06 The review reported that overall trial quality was poor	⟷	Not significant
[34] RCT	25 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 13/15 (87%) with clindamycin plus gentamicin 10/10 (100%) with ciprofloxacin	RR 0.87 95% CI 0.71 to 1.06 The review reported that overall trial quality was poor	⟷	Not significant
[35] RCT	76 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 38/40 (95%) with clindamycin plus gentamicin 33/36 (92%) with ceftazidime plus doxycycline	RR 1.04 95% CI 0.92 to 1.17 The review reported that overall trial quality was poor	⟷	Not significant
[36] RCT	68 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 34/35 (97%) with clindamycin plus gentamicin 33/33 (100%) with ciprofloxacin (plus clindamycin in one women)	RR 0.97 95% CI 0.92 to 1.03 The review reported that overall trial quality was poor	⟷	Not significant
[37] RCT	84 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 40/40 (100%) with clindamycin plus gentamicin 41/44 (93%) with meropenem	RR 1.07 95% CI 0.99 to 1.16 The review reported that overall trial quality was poor	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[38] RCT	77 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 39/40 (98%) with clindamycin plus gentamicin plus doxycycline 37/37 (100%) with imipenem plus cilastin (plus doxycycline in some women)	RR 0.98 95% CI 0.93 to 1.02 The review reported that overall trial quality was poor	⟷	Not significant
[39] RCT	58 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 21/29 (72%) with clindamycin plus gentamicin 23/29 (79%) with cefotaxime	RR 0.91 95% CI 0.68 to 1.22 The review reported that overall trial quality was poor	⟷	Not significant
[40] RCT	30 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 14/14 (100%) with clindamycin plus gentamicin 15/16 (94%) with ciprofloxacin	RR 0.98 95% CI 0.90 to 1.07 Overall effect size RR 1.00 95% CI 0.96 to 1.04 The review reported that overall trial quality was poor	⟷	Not significant
[41] RCT	81 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 10/42 (24%) with amoxicillin/clavulanate 9/39 (25%) with amoxicillin plus aminoglycoside plus metronidazole	RR 1.03 95% CI 0.47 to 2.27 The review reported that overall trial quality was poor	⟷	Not significant
[42] RCT	20 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 2/10 (20%) with ampicillin plus metronidazole 10/10 (100%) with doxycycline plus oxytetracycline/tetracycline plus metronidazole	RR 0.20 95% CI 0.06 to 0.69 The review reported that overall trial quality was poor	●●●	doxycycline plus oxytetracycline/tetracycline plus metronidazole
[43] RCT	44 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 20/22 (91%) with amoxicillin/clavulanate 19/22 (86%) with ampicillin (or amoxicillin) plus gentamicin plus metronidazole	RR 1.05 95% CI 0.85 to 1.30 The review reported that overall trial quality was poor	⟷	Not significant
[44] RCT	60 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 28/30 (93%) with ampicillin 28/30 (93%) with cefoxitin	RR 1.00 95% CI 0.87 to 1.14 The review reported that overall trial quality was poor	⟷	Not significant
[45] RCT	33 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 17/18 (94%) with doxycycline plus amoxicillin/clavulanate 15/15 (100%) with ofloxacin plus amoxicillin/clavulanate	RR 0.94 95% CI 0.84 to 1.06 The review reported that overall trial quality was poor	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[46] RCT	47 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 22/23 (97%) with ampicillin 18/24 (75%) with doxycycline	RR 1.28 95% CI 1.00 to 1.63 Overall effect size RR 1.05 95% CI 0.91 to 1.22 The review reported that overall trial quality was poor	⟷	Not significant
[47] RCT	34 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 14/16 (88%) with imipenem plus cilastatin 18/18 (100%) with meropenem	RR 0.88 95% CI 0.73 to 1.05 The review reported that overall trial quality was poor	⟷	Not significant
[39] RCT	36 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 16/19 (84%) with cefoxitin 14/17 (82%) with cefotaxime	RR 1.02 95% CI 0.76 to 1.37 Overall effect size RR 0.95 95% CI 0.87 to 1.04 The review reported that overall trial quality was poor	⟷	Not significant
[48] RCT	64 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 42/44 (95%) with lymecycline 9/20 (45%) with clindamycin	RR 2.12 95% CI 1.30 to 3.46 The review reported that overall trial quality was poor	●●○	lymecycline
[11] RCT	79 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 40/40 (100%) with azithromycin plus metronidazole 38/39 (97%) with azithromycin	RR 0.89 95% CI 0.50 to 1.57 The review reported that overall trial quality was poor	⟷	Not significant
[49] RCT	36 women In review [19] See Further information on studies for full details of population included in review	**Cure rate** 14/20 (70%) with doxycycline plus metronidazole 15/16 (94%) with ciprofloxacin	RR 0.75 95% CI 0.55 to 1.02 Overall effect size RR 0.80 95% CI 0.52 to 1.24 The review reported that overall trial quality was poor	⟷	Not significant
[20] RCT	741 women with PID, without pelvic or tubo-ovarian abscess	**Resolution of signs and symptoms , 5–24 days post-treatment** 262/289 (90.7%) with ofloxacin plus metronidazole 248/275 (90.2%) with moxifloxacin alone	Difference +0.5% 95% CI –5.7% to +4.0% The review reported that overall trial quality was poor	⟷	Not significant
[21] RCT	669 women with uncomplicated acute PID	**Clinical cure rate (defined as reduction of greater-than or equal to70% in severity score and normal temperature and**	P >0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		leukocyte count) , 2–14 days post-treatment 222/342 (64.7%) with oral moxifloxacin for 14 days 212/326 (65%) with oral doxycycline plus oral metronidazole for 14 days plus one oral ciprofloxacin dose			
[21] RCT	669 women with uncomplicated acute PID	**Clinical success rate (defined as clinical cure or improvement i.e., <70% reduction but >30% plus normal temperature and leukocyte count) , 21–35 days post-treatment** 206/343 (60%) with oral moxifloxacin for 14 days 191/326 (59%) with oral doxycycline plus oral metronidazole for 14 days plus one oral ciprofloxacin dose	P >0.05	⟷	Not significant
[23] RCT	120 women with mild PID treated in an outpatient setting	**Cure rate (defined as absence or reduction of pelvic tenderness as compared to baseline pain levels) , day 14** 42/58 (72%) with doxycycline 56/62 (90%) with azithromycin plus placebo All women received a single intramuscular injection of ceftriaxone.	P = 0.01		azithromycin
[23] RCT	120 women with mild PID treated in an outpatient setting	**Cure rate (defined as reduction of >70% on VAS) , day 14** 23/42 (55%) with doxycycline 35/56 (63%) with azithromycin plus placebo All women received a single intramuscular injection of ceftriaxone.	P = 0.53	⟷	Not significant
[23] RCT	120 women with mild PID treated in an outpatient setting	**Cure rate (defined as reduction of >70% on modified McCormack pain scale) , day 14** 13/42 (31%) with doxycycline 21/56 (38%) with azithromycin plus placebo All women received a single intramuscular injection of ceftriaxone.	P = 0.52	⟷	Not significant
[22] RCT	460 women with PID with no pelvic or tubo-ovarian abscess on pelvic ultrasonography and at laparoscopic examination, not requiring intravenous treatment	**Clinical cure rate (>70% reduction in tenderness score on McCormack scale, apyrexia, and WBC <10,500/mm^3) , 7–14 days post-treatment** 163/228 (71.5%) with oral moxifloxacin for 14 days 171/232 (73.7%) with oral levofloxacin plus oral metronidazole for 14 days All women received a single intramuscular injection of ceftriaxone during days 4–7. Results above are for ITT population. Analysis of per protocol	P >0.05	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		population demonstrated similar results.			
[22] RCT	460 women with PID with no pelvic or tubo-ovarian abscess on pelvic ultrasonography and at laparoscopic examination, not requiring intravenous treatment	**Clinical cure rate (>70% reduction in tenderness score on McCormack scale, apyrexia, and WBC <10,500/mm^3) , 28–42 days post-treatment** 166/228 (72.8%) with oral moxifloxacin for 14 days 169/232 (72.8%) with oral levofloxacin plus oral metronidazole for 14 days All women received a single intramuscular injection of ceftriaxone during days 4–7. Results above are for ITT population. Analysis of per protocol population demonstrated similar results.	Significance not assessed		

Symptom severity

Different antibiotics compared with each other We don't know how different antibiotic regimens compare with each other at reducing symptoms in women with mild PID (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[23] RCT	120 women with mild PID treated in an outpatient setting	**Median VAS pain score (range 0–10) , day 14** 0.8 with doxycycline 0.4 with azithromycin plus placebo All women received a single intramuscular injection of ceftriaxone.	P = 0.23	⟷	Not significant
[23] RCT	120 women with mild PID treated in an outpatient setting	**Median McCormack pain score (range 0–3, total score defined as the sum of individual scores for 12 abdominal and pelvic regions [maximum score = 36]) , day 14** 4 with doxycycline 3 with azithromycin plus placebo All women received a single intramuscular injection of ceftriaxone.	P = 0.59	⟷	Not significant

No data from the following reference on this outcome. [19] [20] [21] [22]

Rate of ectopic pregnancy

No data from the following reference on this outcome. [19] [20] [21] [22] [23]

Fertility

No data from the following reference on this outcome. [19] [20] [21] [22] [23]

Recurrence

Different antibiotics compared with each other We don't know how effective oral moxifloxacin and oral levofloxacin plus oral metronidazole are, compared with each other, at improving recurrence rates at 28–42 days post-treatment in women with confirmed PID (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[22] RCT	460 women with PID with no pelvic or tubo-ovarian abscess on pelvic ultrasonography and at laparoscopic examination, not requiring intravenous treatment	**Clinical recurrence/relapse (defined as reappearance of signs and symptoms of PID) , 28–42 days post-treatment** 18/228 (7.9%) with oral moxifloxacin for 14 days 19/232 (8.2%) with oral levofloxacin plus oral metronidazole for 14 days All women received a single intramuscular injection of ceftriaxone during days 4–7. Results above are for ITT population. Analysis of per protocol population demonstrated similar results.	Significance not assessed		

No data from the following reference on this outcome. [19] [20] [21] [23]

Rate of transmission to others

No data from the following reference on this outcome. [19] [20] [21] [22] [23]

Quality of life

No data from the following reference on this outcome. [19] [20] [21] [22] [23]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects (global)					
[28] RCT	138 women In review [19]	**Adverse effect (any)** 52/69 (75%) with ceftriaxone plus doxycycline 57/69 (83%) with ciprofloxacin plus clindamycin	Significance not assessed		
[30] RCT	272 women In review [19]	**Adverse effects (any)** 20/134 (15%) with cefoxitin plus probenecid plus doxycycline	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		9/138 (7%) with ofloxacin			
[33] RCT	72 women In review [19]	**Adverse effects (any)** 9/35 (26%) with cefoxitin plus probenecid plus doxycycline 6/37 (26%) with ofloxacin	Significance not assessed		
[41] RCT	81 women In review [19]	**Adverse effect (any)** 5/42 (12%) with amoxicillin/clavulanate 2/39 (5%) with amoxicillin plus aminoglycoside plus metronidazole	Significance not assessed		
[49] RCT	36 women In review [19]	**Adverse effect (any)** 11/20 (55%) with doxycycline 3/16 (19%) with metronidazole	Significance not assessed		
[11] RCT	213 women In review [19]	**Adverse effect (any)** 32/107 (30%) with azithromycin plus metronidazole 26/106 (25%) with azithromycin	Significance not assessed		
[25] RCT	170 women In review [19]	**Vestibular disturbance** 0/82 (0%) with cefoxitin plus doxycycline 3/88 (3%) with clindamycin plus gentamicin	Significance not assessed		
[25] RCT	120 women In review [19]	**Surgical intervention** 1/60 (2%) with cefoxitin plus doxycycline 1/60 (2%) with clindamycin plus gentamicin	Significance not assessed		
[21] RCT	669 women with uncomplicated acute PID	**Incidence of drug-related adverse event , 2–14 days post-treatment** 151/343 (44%) with oral moxifloxacin for 14 days 162/326 (50%) with oral doxycycline for 14 days plus one oral ciprofloxacin dose	P = 0.14	⟷	Not significant
Withdrawal from treatment owing to adverse effects					
[28] RCT	138 women In review [19]	**Withdrawal from treatment** 1/69 (1%) with ceftriaxone plus doxycycline 1/69 (1%) with ciprofloxacin plus clindamycin Reason for withdrawal from ceftriaxone plus doxycycline arm given as GI disturbance	Significance not assessed		
[35] RCT	80 women In review [19]	**Withdrew from study** 0/40 (0%) with clindamycin plus gentamicin 0/40 (0%) with ceftazidime plus doxycycline	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] RCT	120 women In review [19]	**Withdrew from study due to adverse effects** 0/60 (0%) with cefoxitin plus doxycycline 1/60 (2%) with clindamycin plus gentamicin Reason for withdrawal from clindamycin plus gentamicin arm given as GI disturbance	Significance not assessed		
[26] RCT	230 women In review [19]	**Withdrew from study due to adverse effects** 1/114 (1%) with cefoxitin plus doxycycline 0/116 (0%) with clindamycin plus gentamicin Reason for withdrawal from cefoxitin plus doxycycline arm given as GI disturbance	Significance not assessed		
[41] RCT	81 women In review [19]	**Withdrawal from treatment due to adverse effects** 0/42 (0%) with amoxicillin/clavulanate 1/39 (3%) with amoxicillin plus aminoglycoside plus metronidazole	Significance not assessed		
[45] RCT	33 people In review [19]	**Withdrawal from treatment due to adverse effects** 0/15 (0%) with amoxicillin/clavulanate 0/18 (0%) with ofloxacin	Significance not assessed		
[49] RCT	36 women In review [19]	**Withdrawal from treatment due to adverse effects** 0/20 (0%) with doxycycline 0/16 (0%) with metronidazole	Significance not assessed		
[11] RCT	213 women In review [19]	**Withdrawn from treatment due to adverse effects** 4/107 (4%) with azithromycin plus metronidazole 2/106 (2%) with azithromycin	Significance not assessed		
[22] RCT	460 women with PID with no pelvic or tubo-ovarian abscess on pelvic ultrasonography and at laparoscopic examination, not requiring intravenous treatment	**Withdrawn from treatment due to at least 1 drug-related event** 4% with oral moxifloxacin for 14 days 5% with oral levofloxacin plus oral metronidazole for 14 days All women received a single intramuscular injection of ceftriaxone during days 4–7.	Significance not assessed		
Angio-oedema					
[41] RCT	81 women In review [19]	**Angio-oedema** 0/42 (0%) with amoxicillin/clavulanate 1/39 (3%) with amoxicillin plus aminoglycoside plus metronidazole	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Allergy					
[29] RCT	148 women In review [19]	**Rash** 2/75 (3%) with cefoxitin plus doxycycline 1/75 (1%) with clindamycin plus tobramycin	Significance not assessed		
[30] RCT	272 women In review [19]	**Rash** 1/134 (0.7%) with cefoxitin plus probenecid plus doxycycline 2/138 (1.4%) with ofloxacin	Significance not assessed		
[21] RCT	669 women with uncomplicated acute PID	**Incidence of drug-related rash , 2–14 days post-treatment** 8/343 (2%) with oral moxifloxacin for 14 days 10/326 (3%) with oral doxycyline plus oral metronidazole for 14 days plus one oral ciprofaloxacin dose	Significance not assessed		
[27] RCT	130 women In review [19]	**Mild rash** 1/67(2%) with cefoxitin pus doxycycline 1/63 (2%) with clindamycin plus gentamicin	Significance not assessed		
[33] RCT	72 women In review [19]	**Allergy** 0/35 (0%) with cefoxitin plus probenecid plus doxycycline 1/37 (3%) with ofloxacin	Significance not assessed		
[36] RCT	70 women In review [19]	**Allergies** 0/35 (0%) with clindamycin plus gentamicin 2/35 (6%) with ciprofloxacin (plus clindamycin in 1 woman)	Significance not assessed		
[43] RCT	44 women In review [19]	**Cutaneous allergy** 1/22 (5%) with amoxicillin/clavulanate 0/22 (0%) with ampicillin (or amoxicillin) plus gentamicin plus metronidazole	Significance not assessed		
[26] RCT	230 women In review [19]	**Pruritus** 2/114 (2%) with cefoxitin plus doxycycline 11/116 (9%) with clindamycin plus gentamicin	Significance not assessed		
Gastrointestinal					
[25] RCT	170 women In review [19]	**Gastrointestinal** 10/82 (12%) with cefoxitin plus doxycycline 15/88 (17%) with clindamycin plus gentamicin	Significance not assessed		
[20] RCT	741 women	**Gastrointestinal** 54/378 (14%) with moxifloxacin	P = 0.057	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		71/363 (20%) with ofloxacin plus metronidazole			
[21] RCT	669 women with uncomplicated acute PID	**Incidence of any drug-related gastro-intestinal adverse events , 2–14 days post-treatment** 100/343 (29%) with oral moxifloxacin for 14 days 149/326 (46%) with oral doxycycline plus oral metronidazole for 14 days plus one oral ciprofloxacin dose	P = 0.001		oral moxifloxacin
[27] RCT	130 women In review [19]	**Diarrhoea** 2/67 (3%) with cefoxitin plus doxycycline 2/63 (3%) with clindamycin plus gentamicin	Significance not assessed		
[21] RCT	669 women with uncomplicated acute PID	**Incidence of any drug-related diarrhoea , 2–14 days post-treatment** 26/343 (8%) with oral moxifloxacin for 14 days 24/326 (7%) with oral doxycycline plus oral metronidazole for 14 days plus one oral ciprofloxacin dose	Significance not assessed		
[22] RCT	460 women with PID with no pelvic or tubo-ovarian abscess on pelvic ultrasonography and at laparoscopic examination, not requiring intravenous treatment	**Incidence of nausea , 28–42 days post-treatment** 42/228 (18.7%) with oral moxifloxacin for 14 days 53/232 (23%) with oral levofloxacin plus oral metronidazole for 14 days All women received a single intramuscular injection of ceftriaxone during days 4–7.	Significance not assessed		
[30] RCT	272 women In review [19]	**Nausea/vomiting** 19/134 (14%) with cefoxitin plus probenecid plus doxycycline 2/138 (1%) with ofloxacin	Significance not assessed		
[33] RCT	72 women In review [19]	**Nausea/vomiting** 3/35 (9%) with cefoxitin plus probenecid plus doxycycline 2/37 (5%) with ofloxacin	Significance not assessed		
[21] RCT	669 women with uncomplicated acute PID	**Incidence of drug-related nausea , 2–14 days post-treatment** 57/343 (17%) with oral moxifloxacin for 14 days 79/326 (24%) with oral doxycycline plus oral metronidazole for 14 days plus one oral ciprofloxacin dose	Significance not assessed		
[21] RCT	669 women with uncomplicated acute PID	**Incidence of drug-related vomiting , 2–14 days post-treatment** 13/343 (4%) with oral moxifloxacin for 14 days	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		36/326 (11%) with oral doxycycline plus oral metronidazole for 14 days plus one oral ciprofloxacin dose			
[22] RCT	460 women with PID with no pelvic or tubo-ovarian abscess on pelvic ultrasonography and at laparoscopic examination, not requiring intravenous treatment	**Incidence of vomiting , 28–42 days post-treatment** 6/228 (2.7%) with oral moxifloxacin for 14 days 15/232 (6.5%) with oral levofloxacin plus oral metronidazole for 14 days All women received a single intramuscular injection of ceftriaxone during days 4–7.	Significance not assessed		
[22] RCT	460 women with PID with no pelvic or tubo-ovarian abscess on pelvic ultrasonography and at laparoscopic examination, not requiring intravenous treatment	**Incidence of upper abdominal pain , 28–42 days post-treatment** 9/228 (4%) with oral moxifloxacin for 14 days 13/232 (5.7%) with oral levofloxacin plus oral metronidazole for 14 days All women received a single intramuscular injection of ceftriaxone during days 4–7.	Significance not assessed		
Headaches/insomnia					
[30] RCT	272 women In review [19]	**Insomnia** 0/134 (0%) with cefoxitin plus probenecid plus doxycycline 2/138 (1%) with ofloxacin	Significance not assessed		
[33] RCT	72 women In review [19]	**Headaches** 0/35 (0%) with cefoxitin plus probenecid plus doxycycline 1/37 (3%) with ofloxacin	Significance not assessed		
Candidal vaginitis					
[30] RCT	272 women In review [19]	**Candidal vaginitis** 6/134 (4%) with cefoxitin plus probenecid plus doxycycline 5/138 (4%) with ofloxacin	Significance not assessed		
[33] RCT	72 women In review [19]	**Candidal vaginitis** 2/35 (6%) with cefoxitin plus probenecid plus doxycycline 1/37 (3%) with ofloxacin	Significance not assessed		
Severe adverse effects					
[11] RCT	213 women In review [19]	**Severe adverse effects** 8/107 (7%) with azithromycin plus metronidazole 2/106 (2%) with azithromycin	Significance not assessed		
[22] RCT	460 women with PID with no pelvic or tubo-ovarian abscess on pelvic ul-	**Incidence of serious adverse events , 28–42 days post-treatment**	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	trasonography and at laparoscopic examination, not requiring intravenous treatment	3/228 (1.3%) with oral moxifloxacin for 14 days 1/232 (0.4%) with oral levofloxacin plus oral metronidazole for 14 days All women received a single intramuscular injection of ceftriaxone during days 4–7. Moxifloxacin group: colitis (n = 1), Stevens-Johnson syndrome (n = 1; identified as drug-related), miscarriage (n = 1). Levofloxacin/metronidazole group: acute pyelonephritis.			

No data from the following reference on this outcome. [23]

Further information on studies

[19] The review included women who had been either: diagnosed clinically or laparoscopically with PID; treated with any antibiotic combination; and with an outcome measure of clinical care, microbiological care, infertility, ectopic pregnancy, chronic pelvic pain, or any other relevant outcome. The review made no distinction for severity of disease or between intravenous and oral treatment.

Comment:

We found one systematic review (search date 1992, 21 studies), which reported on clinical and microbiological cure rates for various antibiotic regimens in the treatment of pelvic inflammatory disease (PID; see table 3, p 26). [50] The review provided aggregated data on indirect comparisons; aspects of the review were subsequently updated (search date 1997, 26 studies, 1925 women). [51] The earlier version of the review [50] examined all antimicrobial regimens, whereas the updated version [51] focused on anti-anaerobic treatment. The identified studies included case series, and it is not possible to ascertain from the aggregated data published how many studies were RCTs. Inclusion criteria were a diagnosis of PID (clinical, microbiological, laparoscopic, or by endometrial biopsy) and microbiological testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. The review found that antibiotics were effective in relieving the symptoms associated with PID, with clinical and microbiological cure rates of 88% to 100% (see table 2, p 26). The only regimen that seemed to perform less well was oral metronidazole plus doxycycline. However, the studies were of low power, and apparent differences in efficacy may have been confounded by differences in disease severity among studies.

Clinical guide:

We found no RCTs comparing antibiotics versus placebo or no treatment. However, such trials would be considered unethical because there is strong consensus that antibiotic treatments are more effective in women with pelvic inflammatory disease (PID) than no treatment. [52] We found little evidence about treatment of PID of differing severity, the effect of ethnicity, or the effects of tracing sexual contacts (see review on Partner notification). The risks of tubal occlusion and of subsequent infertility relate to the severity of PID before starting treatment. [53] Clinical improvement may not translate into preserved fertility. [54] [55] The inclusion of observational studies in the older systematic review without a sensitivity analysis may compromise the validity of the conclusions. In the review, reliable comparison of different drugs may be confounded by possible differences in disease severity among the included studies.

OPTION ORAL ANTIBIOTICS VERSUS PARENTERAL ANTIBIOTICS

- For GRADE evaluation of interventions for Pelvic inflammatory disease, see table, p 27 .

- Oral antibiotics may be as effective as parenteral antibiotics in reducing symptoms and preserving fertility in women with mild to moderate PID, with fewer adverse effects. However, we don't know the optimal duration of treatment.

Benefits and harms

Oral antibiotics versus parenteral antibiotics:

We found one systematic review [19] containing three RCTs that compared oral versus parenteral antibiotic treatment. [1] [30] [33]

Cure rate

Oral antibiotics compared with parenteral antibiotics Oral antibiotics and parenteral antibiotics may be equally effective at improving cure rate in women with uncomplicated PID (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cure rate					
[30] RCT	249 women with uncomplicated pelvic inflammatory disease (outpatient setting) In review [19]	**Cure rate** with oral ofloxacin with parenteral cefoxitin plus oral doxycycline Absolute results not reported	RR 1.03 95% CI 0.97 to 1.10	⟷	Not significant
[33] RCT	72 women with uncomplicated acute salpingitis (outpatient setting) In review [19]	**Cure rate** with oral ofloxacin with parenteral cefoxitin plus oral doxycycline Absolute results not reported	RR 0.97 95% CI 0.88 to 1.07	⟷	Not significant

No data from the following reference on this outcome. [1]

Symptom severity

Oral antibiotics compared with parenteral antibiotics Oral antibiotics (given as an outpatient treatment) and parenteral antibiotics (given as an inpatient treatment) may be equally effective at improving tenderness, chronic pelvic pain, and endometriosis in women with mild to moderate PID (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[1]	831 women with mild to moderate PID In review [19]	**Tender on exam , 30 days** 69/335 (21%) with single intramuscular dose of cefoxitin plus oral probenecid followed by oral doxycycline (outpatient) 63/324 (18%) with IV cefoxitin plus IV doxycycline followed by oral doxycycline (hospital admission for parenteral antibiotics; inpatient)	P = 0.50	⟷	Not significant
[1] RCT	831 women with mild to moderate PID In review [19]	**Endometritis (on biopsy) , 30 days** 102/222 (46%) with single intramuscular dose of cefoxitin plus oral probenecid followed by oral doxycycline (outpatient) 85/226 (38%) with IV cefoxitin plus IV doxycycline followed by oral doxycycline (hospital admis-	P = 0.09	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		sion for parenteral antibiotics; in-patient)			
[1] RCT	831 women with mild to moderate PID In review [19]	**Tubo-ovarian abscess , 30 days** 4/410 (0.9%) with single intramuscular dose of cefoxitin plus oral probenecid followed by oral doxycycline (outpatient) 12/398 (0.7%) with IV cefoxitin plus IV doxycycline followed by oral doxycycline (hospital admission for parenteral antibiotics; in-patient)	Significance not assessed		
[1] RCT	831 women with mild to moderate PID In review [19]	**Chronic pelvic pain , 35 months** 128/380 (34%) with single intramuscular dose of cefoxitin plus oral probenecid followed by oral doxycycline (outpatient) 110/369 (30%) with IV cefoxitin plus IV doxycycline followed by oral doxycycline (hospital admission for parenteral antibiotics; in-patient)	OR 1.24 95% CI 0.87 to 1.77	⟷	Not significant

No data from the following reference on this outcome. [30] [33]

Rate of ectopic pregnancy

Oral antibiotics compared with parenteral antibiotics Oral antibiotics (given as an outpatient treatment) and parenteral antibiotics (given as an inpatient treatment) are equally effective at reducing rate of ectopic pregnancy in women with mild to moderate PID (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of ectopic pregnancy					
[1] RCT	831 women with mild to moderate PID In review [19]	**Ectopic pregnancy , 35 months** 4/410 (1%) with single intramuscular dose of cefoxitin plus oral probenecid followed by oral doxycycline (outpatient) 1/398 (0.3%) with IV cefoxitin plus IV doxycycline followed by oral doxycycline (hospital admission for parenteral antibiotics; in-patient)	OR 3.66 95% CI 0.40 to 33.12	⟷	Not significant

No data from the following reference on this outcome. [30] [33]

Fertility

Oral antibiotics compared with parenteral antibiotics Oral antibiotics (given as an outpatient treatment) and parenteral antibiotics (given as an inpatient treatment) may be equally effective at improving pregnancy or reducing infertility at 35 months in women with mild to moderate PID (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pregnancy					
[1] RCT	831 women with mild to moderate PID In review [19]	**Pregnancy , 35 months** 174/410 (42%) with single intramuscular dose of cefoxitin plus oral probenecid followed by oral doxycycline (outpatient) 166/398 (42%) with IV cefoxitin plus IV doxycycline followed by oral doxycycline (hospital admission for parenteral antibiotics; inpatient)	Significance not assessed		
Infertility					
[1] RCT	831 women with mild to moderate PID In review [19]	**Infertility , 35 months** 71/385 (18.4%) with single intramuscular dose of cefoxitin plus oral probenecid followed by oral doxycycline (outpatient) 67/347 (17.9%) with IV cefoxitin plus IV doxycycline followed by oral doxycycline (hospital admission for parenteral antibiotics; inpatient)	OR 1.32 95% CI 0.86 to 2.04	⟷	Not significant

No data from the following reference on this outcome. [30] [33]

Recurrence

Oral antibiotics compared with parenteral antibiotics Oral antibiotics (given as an outpatient treatment) and parenteral antibiotics (given as an inpatient treatment) may be equally effective at reducing recurrence of PID at 35 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Recurrence					
[1] RCT	831 women with mild to moderate PID In review [19]	**Recurrent PID , 35 months** 51/410 (12%) with single intramuscular dose of cefoxitin plus oral probenecid followed by oral doxycycline (outpatient) 66/398 (17%) with IV cefoxitin plus IV doxycycline followed by oral doxycycline (hospital admission for parenteral antibiotics; inpatient)	OR 0.69 95% CI 0.43 to 1.09	⟷	Not significant

No data from the following reference on this outcome. [30] [33]

Rate of transmission to others

No data from the following reference on this outcome. [1] [30] [33]

Quality of life

No data from the following reference on this outcome. [1] [30] [33]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] RCT	249 women with uncomplicated pelvic inflammatory disease In review [19]	**Adverse effects** 7% with oral ofloxacin 15% with parenteral cefoxitin plus oral doxycycline Absolute numbers not reported Adverse effects included nausea, thrombocytosis, candidal vaginitis, eosinophilia, monocytosis, headaches, and allergy	P <0.2	⟷	Not significant
[33] RCT	72 women with uncomplicated acute salpingitis In review [19]	**Adverse effects** 16% with oral ofloxacin 26% with parenteral cefoxitin plus oral doxycycline Absolute numbers not reported Adverse effects included nausea, thrombocytosis, candidal vaginitis, eosinophilia, monocytosis, headaches, and allergy	Significance not assessed		
[1] RCT	831 women with mild to moderate PID In review [19]	**Adverse drug reaction** 7/410 (1.7%) with single intramuscular dose of cefoxitin plus oral probenecid followed by oral doxycycline (outpatient) 6/398 (1.5%) with admission for parenteral antibiotics (inpatient) Types of adverse event not reported	Significance not assessed		
[1] RCT	831 women with mild to moderate PID In review [19]	**Phlebitis , 30 days** 0/410 (0%) with single intramuscular dose of cefoxitin plus oral probenecid followed by oral doxycycline (outpatient) 14/398 (3%) with IV cefoxitin plus IV doxycycline followed by oral doxycycline (hospital admission for parenteral antibiotics; inpatient)	Significance not assessed		

Comment: **Clinical guide:**
Parenteral administration is indicated in people with severe PID (i.e., those with severe systemic symptoms or tubo-ovarian abscess), those who cannot tolerate fluids orally, and those with any other factor for hospitalisation (e.g., diagnostic uncertainty, pregnant or adolescent people, when severe disease precludes outpatient management, in people unable to follow or tolerate an outpatient regimen, in people who have not responded to outpatient therapy, when clinical follow-up cannot be arranged).

Parenteral treatment as an inpatient offers no advantage over outpatient treatment in women with mild-to-moderate pelvic inflammatory disease (defined as the absence of a tubo-ovarian abscess).

OPTION DIFFERENT DURATIONS OF ANTIBIOTIC TREATMENT

- For GRADE evaluation of interventions for Pelvic inflammatory disease, see table, p 27 .
- We found no direct information about optimal durations of antibiotic treatment in women with PID. A 14-day treatment course is currently recommended.

Benefits and harms

Different durations of antibiotics versus each other:

We identified two systematic reviews that assessed the effects of different antibiotic regimens in the treatment of PID. [19] [51] Neither review assessed the effect of duration of treatment on clinical outcomes, although the most common treatment period was 14 days.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[51] Systematic review	Number of people not reported	**Adverse effects , 2 weeks** with metronidazole plus doxycycline The review reported that significant adverse effects such as pseudomembranous colitis, neuropathy, and drug reactions occur rarely (0.1%–0.5% of cases), and that minor adverse effects such as nausea, flushing, and metallic taste, occur in 30% to 50% of people after two weeks' treatment with metronidazole plus doxycycline			

No data from the following reference on this outcome. [19]

Comment: **Clinical guide:**
A 14-day treatment course is recommended for pelvic inflammatory disease based on the current evidence.

QUESTION What are the effects of routine antibiotic prophylaxis to prevent pelvic inflammatory disease before IUD insertion?

OPTION ROUTINE ANTIBIOTIC PROPHYLAXIS BEFORE IUD INSERTION IN WOMEN AT HIGH RISK

- For GRADE evaluation of interventions for Pelvic inflammatory disease, see table, p 27 .
- We found no direct information from RCTs about antibiotic prophylaxis before IUD insertion in women at high risk of pelvic inflammatory disease.
- Risks of PID may be increased after instrumentation of the cervix, and testing for infection before such procedures is advisable, but we don't know whether prophylactic antibiotics before IUD insertion reduce these risks.

Benefits and harms

Antibiotic prophylaxis before IUD insertion in women at high risk:

We found no RCTs on the effects of routine antibiotic prophylaxis in women at high risk of pelvic inflammatory disease.

Comment: Nausea and vomiting has been reported with 17% to 28% of healthy volunteers on doxycycline, depending on the formulation given. [56]

See the harms section of Antibiotics (for symptoms and microbiological clearance in women with confirmed pelvic inflammatory disease), p 3 .

OPTION ROUTINE ANTIBIOTIC PROPHYLAXIS BEFORE IUD INSERTION IN WOMEN AT LOW RISK

- For GRADE evaluation of interventions for Pelvic inflammatory disease, see table, p 27 .
- Risks of PID may be increased after instrumentation of the cervix, and testing for infection before such procedures is advisable, but prophylactic antibiotics in women at low risk of PID seem no more effective than placebo at reducing rate of PID.

Benefits and harms

Antibiotic prophylaxis before IUD insertion versus no antibiotic prophylaxis (in women at low risk):

We found one systematic review (search date 2012, 6 RCTs, 5797 women requesting IUD insertion). [57]

Rate of PID

Antibiotic prophylaxis before IUD insertion versus no antibiotic prophylaxis (in women at low risk) Antibiotic prophylaxis before IUD insertion seems no more effective than placebo or no treatment at reducing the incidence of pelvic inflammatory disease in women at low risk of PID (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Rate of PID					
[57] Systematic review	5797 women requesting IUD insertion 6 RCTs in this analysis	**Incidence of PID** 27/2906 (0.9%) with single dose of doxycycline or azithromycin (1 hour before IUD insertion) 30/2891 (1.0%) with placebo (1 hour before IUD insertion) or no treatment The rate of PID in all women was low (0.5%–1.6%), regardless of whether they received antibiotics, suggesting that this was a low-risk group	RR 0.89 95% CI 0.53 to 1.50 The wide confidence interval suggests that the study may have lacked power to detect a clinically important difference	⟷	Not significant

Further information on studies

Comment: Nausea and vomiting has been reported with 17% to 28% of healthy volunteers on doxycycline, depending on the formulation given. [56]

See the harms section of Antibiotics (for symptoms and microbiological clearance in women with confirmed pelvic inflammatory disease), p 3 .

Clinical guide:
In the populations included in the systematic review, the risk of PID after IUD insertion was low. [57] The occurrence of PID in this group usually reflects the introduction of infection into the uterus during IUD insertion, and will therefore vary with the prevalence of STDs in the population. A further systematic review also found that the absolute risk of PID was low even when gonorrhoea or chlamydia was present at the time of IUD insertion (0%–5% for those with an STD compared with 0%–2% in those without an STD). [58]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antibiotics (for symptoms and microbiological clearance in women with confirmed pelvic inflammatory disease) Three RCTs added; [21] [23] [22] categorisation unchanged (likely to be beneficial).

Routine antibiotic prophylaxis before IUD insertion in women at low risk One previously included systematic review updated and new data added. [57] Categorisation unchanged (unlikely to be beneficial).

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Disclaimer

TABLE 1 **RCTs comparing outpatient versus inpatient antibiotic treatment for PID at different follow-up periods (see text, p 3).** [1] [18]

Ref	Population	Recurrence	Chronic pelvic pain	Infertility	Ectopic pregnancy
[1]	831 women with mild to moderate PID; 808 followed up to 35 months; inpatients *v* outpatients	12% *v* 17%; OR 0.69, 95% CI 0.43 to 1.09	34% *v* 30%; OR 1.24, 95% CI 0.87 to 1.77	18.4% *v* 17.9%; OR 1.32, 95% CI 0.86 to 2.04	1.0% *v* 0.3%; OR 3.66, 95% CI 0.40 to 33.12
[18]	As above; 541 followed up to 84 months; inpatients *v* outpatients	18% *v* 24%; OR 0.71, 95% CI 0.48 to 1.05	41% *v* 45%; OR 1.21, 95% CI 0.87 to 1.67	17% *v* 21%; OR 0.88, 95% CI 0.59 to 1.32	1.2% *v* 0.2%; OR 4.91, 95% CI 0.57 to 42.25

PID, pelvic inflammatory disease

TABLE 2 **Standard antibiotic regimens and corresponding trial evidence (see text, p 3).** [19]

Regimen	Trial evidence available
Oral ofloxacin 800 mg daily plus oral metronidazole 800 g daily for 14 days	Ofloxacin plus metronidazole *v* clindamycin plus gentamicin
im ceftriaxone 250 mg once or im cefoxitin 2 g once plus oral probenecid 1 g once followed by oral doxycycline 200 mg daily plus oral metronidazole 800 mg daily for 14 days	Cefoxitin plus doxycycline *v* cefoxitin plus probenecid plus doxycycline
im ceftriaxone 250 mg or im cefoxitin 2 g plus oral probenecid 1 g or a third-generation cephalosporin plus oral doxycycline 200 mg for 14 days	Ceftriaxone or cefoxitin plus oral probenecid or a third-generation cephalosporin plus oral doxycycline *v* non-standard treatments
iv cefoxitin 6 g daily plus iv (or oral) doxycycline 200 mg daily followed by oral doxycycline 200 mg daily plus oral metronidazole 800 mg daily to complete 14 days	Cefoxitin plus doxycycline *v* clindamycin plus gentamicin, cefoxitin plus doxycycline *v* cefoxitin plus probenecid plus doxycycline
iv clindamycin 2.7 g daily plus iv gentamicin 2 mg/kg loading dose then 4.5 mg/kg daily followed by either oral doxycycline 200 mg daily plus oral metronidazole 200 mg daily or oral clindamycin 1.8 g daily to complete 14 days	Ofloxacin plus metronidazole *v* clindamycin plus gentamicin, cefoxitin plus doxycycline *v* clindamycin plus gentamicin, iv clindamycin plus gentamicin followed by either oral doxycycline plus oral metronidazole or oral clindamycin *v* non-standard treatments
iv ofloxacin 800 mg daily plus iv metronidazole 1.5 g daily for 14 days	Ofloxacin plus metronidazole *v* clindamycin plus gentamicin
iv ciprofloxacin 400 mg daily plus iv (or oral) doxycycline 200 mg daily plus iv metronidazole 1.5 g daily (unspecified length, presume 14 days)	No RCT comparisons

im, intramuscular; iv, intravenous

TABLE 3 **Cure rates for the antibiotic treatment of acute PID: aggregated data from a systematic review of RCTs and case series (see text, p 3).** [50] [51]

Drug regimen	Number of studies	Number of women	Cure rate (%)	
			Clinical	Microbiological*
Inpatient treatment (initially parenteral switching to oral)				
Clindamycin plus aminoglycoside	11	470	91	97
Cefoxitin plus doxycycline	8	427	91	98
Cefotetan plus doxycycline	3	174	95	100
Ceftizoxime plus tetracycline	1	18	88	100
Cefotaxime plus tetracycline	1	19	94	100
Ciprofloxacin	4	90	94	96
Ofloxacin	1	36	100	97
Sulbactam/ampicillin plus doxycycline	1	37	95	100
Co-amoxiclav	1	32	93	–
Metronidazole plus doxycycline	2	36	75	71
Outpatient treatment (oral unless indicated otherwise)				
Cefoxitin (im) plus probenecid plus doxycycline	3	219	89	93
Ofloxacin	2	165	95	100
Co-amoxiclav	1	35	100	100
Sulbactam/ampicillin	1	36	70	70
Ceftriaxone (im) plus doxycycline	1	64	95	100
Ciprofloxacin plus clindamycin	1	67	97	94

**Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or both, when detected in lower genital tract; im, intramuscular; PID, pelvic inflammatory disease

GRADE **Evaluation of interventions for Pelvic inflammatory disease.**

Important outcomes	Cure rate, Fertility, Quality of life, Rate of ectopic pregnancy, Rate of PID, Rate of transmission to others, Recurrence, Symptom severity								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
How do different antimicrobial regimens compare when treating women with confirmed pelvic inflammatory disease?									
at least 35 RCTs (at least 4289 women) [19] [20] [21] [22] [23]	Cure rate	Different antibiotics versus each other	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and for poor quality studies; directness point deducted for unclear disease severity/regimens used
1 (120) [23]	Symptom severity	Different antibiotics versus each other	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for short follow-up
1 (460) [22]	Recurrence	Different antibiotics versus each other	4	–1	0	–1	0	Low	Quality points deducted for incomplete reporting of results; directness point deducted due to short-term follow-up (unclear whether recurrence or relapse)
2 (321) [30] [33]	Cure rate	Oral antibiotics versus parenteral antibiotics	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for inclusion of oral antibiotics in parenteral arm
1 (831) [1]	Symptom severity	Oral antibiotics versus parenteral antibiotics	4	–1	0	–1	0	Low	Quality point deducted for no statistical assessment. Directness point deducted for inclusion of intramuscular injection in outpatient arm and oral antibiotics in parenteral arm
1 (831) [1]	Rate of ectopic pregnancy	Oral antibiotics versus parenteral antibiotics	4	–1	0	–1	0	Low	Quality point deducted for no statistical assessment. Directness point deducted for inclusion of intramuscular injection in outpatient arm
1 (831) [1]	Fertility	Oral antibiotics versus parenteral antibiotics	4	–1	0	–1	0	Low	Quality point deducted for no statistical assessment for some outcomes. Directness point deducted for inclusion of intramuscular injection in outpatient arm
1 (831) [1]	Recurrence	Oral antibiotics versus parenteral antibiotics	4	–1	0	–1	0	Low	Quality point deducted for no statistical assessment. Directness point deducted for inclusion of intramuscular injection in outpatient arm
What are the effects of routine antibiotic prophylaxis to prevent pelvic inflammatory disease before IUD insertion?									
6 (5797) [57]	Rate of PID	Antibiotic prophylaxis before IUD insertion versus no antibiotic prophylaxis (in women at low risk)	4	0	0	–1	0	Moderate	Directness point deducted for small number of events

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.